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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Lisbeth Illum

Serial No.: 08/359,937 Group Art Unit: 1502

Bet 2-25-97

Filed: December 20, 1994 Examiner: G. Kishore

For: SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY

Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT

Sir:

Responsive to the Office Action mailed from the U.S. Patent Office on September 27, 1996, Applicants request a one month extension of time for response. A Petition for a one month extension of time and the appropriate fee are enclosed.

Rejections Under the Doctrine of Obviousness-Type Double Patenting

Claims 1-10 and 15-16 were rejected under the doctrine of obviousness-type double patenting as being obvious over claims 1-13 of U.S. Patent No. 5,204,108 to Illum.

Claims 1-13 of U.S. Patent No. 5,204,108 are directed to drug delivery compositions suitable for transmucosal delivery, which are substantially free of enhancer, and which include microspheres made of starch, gelatin, collagen or dextran, and a bioactive peptide having a maximum molecular weight of 6000 suitable for systemic administration. Claim 2

defines the microspheres as having a diameter between 10 and 100 microns. Claim 3 requires the microsphere material to be cross-linked; claim 4 defines the microspheres as formed from the drug. Claim 5 is limited to microspheres suitable for administration to the vagina; claim 6 is limited to microspheres suitable for administration to the eye; claim 7 is limited to microspheres suitable for delivery to the nasal mucosa. Claim 9 defines the peptide as having a molecular weight of at least 1000; claim 10 defines the peptide as insulin or calcitonin. Claims 11, 12 and 13 define the microspheres as having drug incorporated therein.

Claims 1-10 and 15-16 of the present application are limited to microspheres of between 0.01 and 10 microns in diameter. Disregarding all other limitations, there is no disclosure in the claims (or for that matter, the specification) of the '108 patent to Illum that would lead one of ordinary skill in the art to select microspheres of 1/10th to 1/100th of the size of the microspheres of the '108 patent. As discussed in more detail below, unexpectedly better systemic delivery was obtained following nasal administration of the claimed microspheres than was obtained with larger diameter microspheres.

The Federal Circuit has held that the mere fact that a broad process claim of the patent reads on or dominates a narrower claim does not, per se, justify a double patenting rejection, and that in the double patenting rejection, the specification of the patent should not be used as prior art. *In re Kaplan*, 789 F.2d 1574, 229 USPQ 678 (Fed. Cir. 1986).

A rejection for "obviousness-type" double patenting should only be made when there is no "patentable difference" between the claims of the application at issue and the claims of the other application or patent. "[A] double patenting of the obviousness type rejection is "analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. §103, except that the patent principally underlying the double patenting rejection is not considered prior art." In re Longi, 759 F.2d 887, 892, n. 4. (Fed. Cir. 1985), *citing* In re Braithwaite, 379 F.2d 594, 600, n. 4 (C.C.P.A. 1967). It is a judicially-created doctrine. General Foods v. Studiengesellschaft Kohle MbH, 972 F.2d 1272, 1278-1279 (Fed. Cir. 1992); In re Braat, 937 F.2d 589, 592 (Fed. Cir. 1991). A proper double patenting rejection must consider the claim as a whole, including all limitations. General Foods, at p. 1278; Carman v. Wahl, 724 F.2d 932, 940 (Fed. Cir. 1983); *cf.* Ex Parte Crissy, 201 U.S.P.Q. (BNA) 689, 693 (P.O.B.A. 1976).

In view of the claims of the '108 patent, there is no suggestion of that which is claimed by the Applicant. It would not have been obvious to substitute microspheres of 1/10th to 1/100th of the size of the microspheres of the '108 patent to Illum, with any expectation of success in systemic drug delivery. In fact, one would be inclined to think that larger, rather than smaller, would achieve greater delivery. Accordingly, the rejection of claims 1-10 and 15-16 under the doctrine of obviousness-type double patenting over claims 1-13 of the '108 patent to Illum should be withdrawn.

Claims 11-14 and 17-28 were rejected under the judicially created doctrine of double patenting over U.S. Patent No. 5,204,108 to Illum.

Claims 11-14 and 17-28 are directed to a system for intranasal administration (claims 11 and 12) and method for intranasal delivery (claims 14 and 17-28). The claims all require the same limitations as claim 1: that the microspheres have a diameter of between 0.1 and 10 microns. The claims are further limited to intranasal delivery, and even more limited in the case of claims 12 and 13 to the use of a container delivering the particles via a gas stream. The '108 patent to Illum does not suggest or disclose the selection of microspheres in the claimed size range, or provide any suggestion to administer them to promote system delivery of a drug. The claims are directed to the patentably distinct subject matter.

Rejections under 35 U.S.C. § 103

Claims 1-6, 11-13 and 16 were rejected under 35 U.S.C. § 103 as being obvious over U.S. Patent No. 4,847,091 to Illum ("Illum"). Claims 1-28 were rejected under 35 U.S.C. § 103 as obvious over Illum in view of PCT WO 88/09163 by Illum (Illum PCT).

Claims 1-28 were rejected under 35 U.S.C. § 103 as obvious over Illum, L., *Nato ASI Symposium*, 125:205-210 (1986) ("Illum (1986)"). Claims 1-28 also were rejected under 35 U.S.C. § 103 as being obvious over Illum in view of Hanson *et al.*, *Advanced Delivery Systems for Peptides and Proteins*, p. 233-242 (1988) ("Hanson"), or Salzman *et al.*, *New Eng. J. Med.*, 312:1078-1084 (1985) ("Salzman"), or vice versa. Claims 7-12, 14 and 23-26

were rejected under 35 U.S.C. § 103 as obvious over Illum (1986) in view of Hanson or Salzman or vice versa.

Illum and Illum PCT

Illum discloses microspheres incorporating sodium cromoglycate which are formed of a material having ion exchange properties. The disclosure of Illum is limited to the synthesis of microspheres incorporating sodium cromoglycate and the use of the microspheres for local treatment. Illum discloses that the microspheres can be used for treatment of allergic conditions. For example, Illum discloses treatment of conditions of the outer eye such as hay fever or conjunctivitis (col. 3, lines 3-20), conditions of the nose such as perennial rhinitis, and conditions of the lung such as asthma. The disclosure of Illum thus is limited to the administration of microspheres for localized treatment of a condition. Nothing in Illum teaches or suggests the use of the sodium cromoglycate containing microspheres for systemic therapeutic treatment.

Illum PCT relates to drug delivery systems including microsphere particles containing an active drug and a surfactant which enhances uptake of the active drug. Illum PCT does not teach or suggest the particulate drug delivery systems claimed, wherein at least 90 wt % of the microspheres have a diameter between 0.1 μm and 10 μm, and wherein the composition is capable of systemic delivery of a therapeutically effective amount of the drug upon nasal administration. The composition disclosed by Illum PCT requires the presence of a surfactant to promote uptake of the drug. Illum PCT provides no motivation to select

microparticles of the claimed diameter to promote the absorption of wide range of drugs including peptides, even in the absence of an enhancer, as claimed.

As noted in the Applicant's Supplemental Response filed May 26, 1994 in the parent application, sodium cromoglycate is poorly absorbed and not useful for systemic treatment. Rather, sodium cromoglycate is used therapeutically for local treatment. As indicated in the Supplemental Response filed May 26, 1994, and in the documents cofiled therewith, sodium cromoglycate is poorly absorbed from the gastrointestinal tract and considered only to be effective when administered for local action. It is used for the treatment of asthma, rhinitis and nasal congestion, which are clearly localized therapeutic treatment applications. The prior art does not suggest that sodium cromoglycate could be delivered systemically upon nasal administration, and in fact suggests that it could not.

The Applicant has provided evidence including literature articles, in Applicant's Supplemental Response mailed May 26, 1994, indicating that sodium cromoglycate is known to those skilled in the art to be poorly absorbed and to be therapeutically effective only when administered topically for local action. For example, Katzung, Bertram G., "Basic & Clinical Pharmacology," Lange Medical Publications, Los Altos, CA 94022, 1984, states on page 228 that "cromolyn is poorly absorbed from the gastrointestinal tract. For use in asthma, it must be applied topically," and states on page 230 that "because it is so poorly absorbed, adverse effects of cromolyn are minor and are localized in the sites of deposition." Similarly, Martindale (*Extra Pharmacopoeia*, Vol. 30, p. 1142) also enclosed with

Applicant's Supplemental Response mailed May 26, 1994 states that sodium cromoglycate is "poorly absorbed" and that "less than 7% of an intranasal dose is absorbed".

Thus, nothing in Illum, or in the literature in the area of drug delivery, indicates that the compositions disclosed by Illum, including microspheres and sodium cromoglycate, could be administered intranasally to systemically deliver a therapeutically effective amount of a drug. There is no indication that there is systemic delivery with the Illum compositions. There further is no indication that there is systemic delivery of a therapeutically effective amount of a drug using the Illum compositions.

While the Examiner has alleged that it is possible that systemic delivery of sodium chromoglycate may occur, there is no support for this allegation in the prior art, and, in fact, the prior art teaches away from such a conclusion. The ultimate legal conclusion of obviousness must be based on facts or records, not on unsupported allegations. *In re Wagner et al.* (CCPA 1967) 371 F.2d 877, 152 USPQ 552.

The Applicant has demonstrated the synthesis and use of compositions including microspheres which are capable of systemic delivery of a therapeutically effective amount of a drug in a mammal. The Applicant further has provided experimental results which show that the compositions are therapeutically effective systemically. For example, the compositions can be intranasally administered to systemically deliver insulin to sheep in a therapeutically effective amount to reduce plasma glucose (see Example 3 and, particularly, page 26 of the specification).

Nothing in the applied art suggests the claimed particulate drug delivery compositions, and methods for their administration claimed, wherein at least 90 wt% of the microspheres have a diameter between 0.1 and 10 μm, and include an active drug, and can be intranasally administered to systemically deliver a therapeutically effective amount of the drug to a mammal, and wherein improved systemic delivery is obtained in comparison to the use of larger particles. Nothing in the applied art alone or in combination suggests the particular embodiments defined by the claims, wherein, for example, the microspheres include a biologically active peptide, such as insulin or calcitonin, and are capable of systemic delivery of a therapeutically active amount of the peptide upon intranasal administration.

Illum (1986)

Illum (1986) discloses albumin starch microspheres for use in nasal administration. The preferred size range of the microspheres is 40-60 μm (page 207 of Illum 1986). Illum (1986) does not teach or suggest the use of microspheres having a diameter less than 20 μm for use in intranasal delivery. Nothing in Illum (1986) would have motivated one of ordinary skill in the art to make or use the claimed microspheres which have a diameter between 0.1 μm and 10 μm. Illum (1986), in fact, teaches away from the claimed microparticles by suggesting specifically the use of microspheres with a size of 40-60 μm. In view of Illum (1986), there would have been no motivation to make the claimed microspheres.

The Applicant has demonstrated that, unexpectedly, improved systemic therapeutic results are obtained by intranasal administration of microspheres having a diameter less than 10 μm, which is not suggested in the cited art (see Example 1 of the specification). All of the microspheres disclosed in Illum (1986) have a size greater than 10 μm. For example, the albumin microspheres disclosed in Illum (1986) have a swelled size of 40 μm or greater, and since the degree of swelling is 40%, this corresponds to a size of 28 μm or greater. The starch microspheres disclosed in Illum (1986) have a dry volume mean diameter of approximately 20 μm, while the DEAE dextran microspheres obtained from Pharmacia disclosed in Illum (1986) have a quoted dry bead size ranging from 25 to 125 μm. Thus, nothing in Illum 1986 discloses or suggests making or using the claimed microparticles having a diameter between 0.1 and 10 μm. There is no suggestion in Illum (1986) of the advantages and features of the use of lower diameter microspheres as demonstrated by the Applicant.

Example 1 of the above-identified application provides a comparison of the results of intranasal administration of insulin in starch microspheres of diameter greater than 10 μm and less than 10 μm, which shows that a significant increase in blood insulin concentration was obtained using the smaller (less than 10 μm) microspheres. Example 2 demonstrates that microspheres of 1 to 10 μm have a much longer residence time in the nasal cavity than microspheres of 40 μm, which is unexpected. Example 3 shows that improved intranasal absorption of insulin in sheep was obtained using small (less than 10 μm) hyaluronic acid and

hyaluronic acid-dextran microspheres compared to larger microspheres (25 μm) of starch. Applicant further provided additional data, attached as Exhibit 15, together with the Amendment mailed March 21, 1994, in the parent application, demonstrating that the absorption of granulocyte-colony stimulating factor was enhanced using microspheres of 1-10 μm diameter in comparison to larger microspheres.

Thus, nothing in Illum (1986) suggests the unexpected results obtained by the Applicant demonstrating that improved nasal absorption and systemic delivery of a drug can be obtained using microspheres having a diameter between 0.1 and 10 μm. In view of Illum (1986), one of ordinary skill would have had no motivation to practice the claimed methods or make the claimed compositions. One of ordinary skill in the art would have had no motivation to make compositions including microspheres having a size between about 0.1 and 10 μm to improve intranasal absorption of a drug. Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. *In re Vaeck* (CAFC 1991) 947 F.2d 488, 20 PQ2d 1438. In the absence of hindsight, there is no suggestion in Illum (1986) of the methods and compositions claimed.

Hanson and Salzman

Hanson discloses that the biological response to nasal administration of calcitonin can be increased by the addition of various surfactants. Salzman discloses that intranasal absorption of insulin can be increased in the presence of a non-ionic detergent. Nothing in

Hanson or Salzman suggests the use of microspheres. Nothing in either Hanson or Salzman teaches or suggests making bioadhesive microspheres which have a diameter between 0.1 to 10 μm for the intranasal administration and systemic delivery of a drug. In order to make a determination of obviousness under 35 U.S.C. § 103, the prior art must suggest the invention claimed. *In re Dow Chemical Company*, 837 F.2d 469 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686 (Fed. Cir. 1987). Nothing in Hanson or Salzman provides any suggestion of the claimed compositions including microspheres, or provides any teaching of methods for making or using the compositions, or any suggestion that they would provide the beneficial effects shown by the Applicant.

The Combined Prior Art

Nothing in Hanson or Salzman, alone or in combination with Illum, Illum PCT and/or Illum (1986), provides any teaching or suggestion of the claimed methods and compositions including microspheres for intranasal administration and systemic delivery of a therapeutically effective amount of a drug. In view of the combined teaches of the applied art, there would have been no motivation or incentive to practice the methods or make the compositions having improved delivery properties claimed.

In view of the applied art and knowledge available in the art, there would have been no motivation to make the compositions for systemic delivery of drugs recited by the claims. There is no suggestion in the applied art of providing a drug delivery composition including microspheres and an active drug, wherein at least 90 wt % of the microspheres of the

composition have a diameter between 0.1 μm and 10 μm, and wherein the composition is capable of delivering systemically a therapeutically effective amount of the drug upon intranasal administration. There further would have been no motivation to provide the different embodiments claimed, wherein, for example, the microspheres are heat stabilized, include an absorption enhancer, or include a biologically active peptide such as insulin or calcitonin. In view of the applied art, one of ordinary skill in the art would not have been motivated to practice the claimed methods or make the claimed compositions, or to expect that they would be effective for systemic delivery of drug upon nasal administration. A valid rejection under 35 U.S.C. § 103 must be based on prior art that indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469 (Fed. Cir. 1988).

The teachings of the applied art and knowledge available in the art would have lead one of ordinary skill away from practicing the claimed methods and making the claimed compositions. One of ordinary skill in the art would not expect that a drug delivery composition including microspheres having a diameter between 0.1 μm and 10 μm could be used for improved intranasal systemic delivery of a therapeutically effective amount of an active drug such as a peptide. As indicated in Gizurarson, *Advanced Drug Delivery Reviews*, Vol. 11, 1993, pp. 331, attached as Exhibit A with Appellant's Amendment mailed March 29, 1996, nasal administration and systemic delivery of protein drugs in a therapeutically effective amount has proved difficult. Gizurarson states that the absorption and delivery of

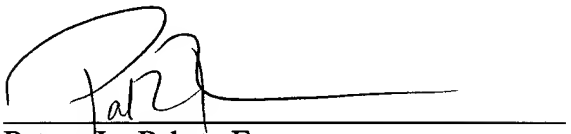
peptides without adversely effecting the physiology of the nose has proved difficult because absorption of peptide drugs across the nasal mucosa is difficult. There is no motivation in the applied art to make a drug delivery system including microspheres having a diameter of between 0.1 to 10 μm for systemic delivery of a peptide drug via nasal administration.

Nothing in the combined applied art suggests the unexpected results discovered by the Applicant. In deciding obviousness one must look at prior art from the vantage point in time prior to when the invention was made; hindsight obviousness after the invention has been made is not the test. *In re Carroll* (CCPA 1979) 601 F.2d 1184, 202 USPQ 571. In the absence of hindsight, it would not have been obvious to one of ordinary skill in the art to make the claimed compositions or to practice the claimed methods.

Conclusion

In view of the above arguments, allowance of each of pending claims 1-28 is respectfully solicited.

Respectfully submitted,



Patrea L. Pabst, Esq.
Registration No. 31,284

Date: January 27, 1997

ARNALL GOLDEN & GREGORY
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8798
(404) 873-8599 (fax)

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Teresa R. Spratt

Date: January 27, 1997

APPENDIX
Pending Claims

1. A particulate drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres and a systemically active drug, wherein at least 90 wt % of the microspheres of the composition have a diameter of between 0.1 μm and 10 μm, and wherein the composition is capable of systemic delivery of a therapeutically effective amount of the drug to a mammal upon intranasal administration.

2. A drug delivery composition according to Claim 1 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

3. A drug delivery composition according to Claim 1 or 2 wherein the microspheres comprise starch, gelatin, albumin, collagen, or dextran.

4. A drug delivery composition according to Claim 3 wherein the microspheres are starch microspheres.

5. A drug delivery composition according to Claim 1 wherein the microsphere material is cross-linked.

6. A drug delivery composition according to Claim 1 wherein the microspheres have been heated to stabilize the microspheres.

7. A drug delivery composition according to Claim 1 additionally comprising an absorption enhancer.

8. A drug delivery composition according to Claim 7 wherein the absorption enhancer is a surfactant.

9. A drug delivery composition according to Claim 1 wherein the drug is a biologically active peptide.

10. A drug delivery composition according to Claim 9 wherein the peptide is insulin or calcitonin.

11. A system for intranasal drug delivery comprising a drug delivery composition according to Claim 1 and a container having an orifice through which the composition can be delivered to the nasal mucosa in a gas stream.

12. A system according to Claim 11 wherein the system is such that, in use, the product of the flow rate and the square of the microsphere aerodynamic diameter is greater than 2000 μm^2.litres/min.

13. A method of delivering a drug to the nasal mucosa, comprising introducing a gas stream containing a composition according to Claim 1 into the nose.

14. A method of treating diabetes comprising introducing a gas stream containing a composition according to Claim 1 wherein the systemically active drug is insulin into the nose.

15. The drug delivery composition of claim 1 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

16. The drug delivery composition of claim 1 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.

17. A method for systemically delivering an active drug to a mammal, the method comprising:

a) providing a composition comprising a plurality of bioadhesive microspheres and an active drug, wherein at least 90 wt % of the microspheres in the composition have a diameter between 0.1 μm and 10 μm; and

b) administering the composition to a mammal intranasally thereby to systemically delivery a therapeutically effective amount of the drug to the mammal.

18. The method of claim 17 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

19. The method of claim 17 wherein the microspheres comprise a material selected from the group consisting of starch, gelatin, albumin, collagen and dextran.

20. The method of claim 19 wherein the microspheres comprise starch.

21. The method of claim 17 wherein the microsphere material is cross-linked prior to step b).

22. The method of claim 17 wherein the microspheres are heated to stabilize the microspheres prior to step b).

23. The method of claim 17 the composition provided in step a) further comprises an absorption enhancer.

24. The method of claim 23 wherein the absorption enhancer is a surfactant.

25. The method of claim 17 wherein the drug is a biologically active peptide.

26. The method of claim 25 wherein the peptide is insulin or calcitonin.

27. The method of claim 17 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

28. The method of claim 17 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.